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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/549,096	04/12/2000	Carl Ware	07246-030001	7342

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/549,096	WARE, CARL	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/19/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,27,36 and 51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-27, 36 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/19/04 has been entered.

2. Claims 26-27, 36 and 51-53 are pending and are being acted upon in this Office Action.

3. The disclosure is objected to because of the following informalities: (1) the Brief Description of the "Figure 3" on page 9, line 14 does not correspond with the FIG. 3A and FIG. **3** itself; (2) The Brief Description of the "Figure 16" on page 12, line 3 does not match with FIG. 16A-16D; (3) The "Figure 22" on page 14, line 16 does not correspond with FIG. 22A-22B. Appropriate action is required.

4. The drawings filed 9/17/02 is objected to because the letter "B" is missing from Figure 3B.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 26-27, 36 and 51-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) A method for inhibiting a p30 polypeptide mediated delayed type hypersensitivity or inflammatory response comprising (a) providing a composition comprising a soluble HVEM polypeptide that binds to a p30 polypeptide and that binding inhibits the binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM, said p30 polypeptide having an apparent molecular weight of about 30 kDa as determined by reducing SDS-PAGE and an isoelectric charge (pI) of about pI 7 to pI 8.5 and that binds HVEM or LTβR; and (b) contacting the cell expressing the cell surface expressed p30 polypeptide with an amount of the composition comprising said soluble HVEM polypeptide sufficient to inhibit a p30 polypeptide mediated delayed type hypersensitivity or inflammatory

response, (2) the said method wherein the cell is contacted with said composition in vivo, (3) the said method wherein the contacted cell expresses p30 polypeptide on its cell surface and the HVEM polypeptide is a recombinant soluble HVEM polypeptide, (4) the said method wherein the soluble HVEM that binds to the p30 polypeptide comprises a fusion protein comprising the extracellular domain of HVEM fused to the Fc region of human IgG, (5) the said method wherein the soluble HVEM that binds to the p30 polypeptide is HVEM-Fc; (6) a method for inhibiting a p30 polypeptide-mediated cellular response comprising (a) providing a composition comprising a soluble HVEM or LTβR polypeptide that binds to a p30 polypeptide and that binding inhibits the binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM, said p30 polypeptide having an apparent molecular weight of about 30 kDa as determined by reducing SDS-PAGE and an isoelectric charge (pI) of about pI 7 to pI 8.5 and that binds HVEM or LTβR; and (b) contacting the cell expressing the cell surface expressed p30 polypeptide with an amount of the composition comprising a soluble HVEM sufficient to inhibit a p30 polypeptide-mediated cellular response, said cellular response comprising inhibition of lymphocyte proliferation in vitro, **does not** reasonably provide enablement for (1) a method of inhibiting a p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis* (claims 26-27, 36, 51-52) by administering a composition comprising *all* HVEM or *all* LTβR polypeptide such as all soluble HVEM polypeptide (claim 36), all fusion protein comprising HVEM or LTβR (claim 51) or all HVEM:Fc or LTβR:Fc polypeptide (claim 52) that binds to a p30 polypeptide having an apparent molecular weight of about 30 kDa as determined by SDS-PAGE and pI of about pI 7 to pI 8.5 that binds to HVEM or LTβR and (2) a method of in inhibiting all p30 polypeptide mediated cellular response in vitro (claim 53). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only administering Fc fusion protein comprising the extracellular domain of mouse HVEM fused to the Fc region of human IgG (HVEM:Fc or soluble HVEM polypeptide) to eight weeks old female BDF1 mice that has been immunized with OVA absorbed to alum inhibits inflammation or delayed-type hypersensitivity in mice as measured by increased footpad thickness (page 56, Figure 9). The specification further discloses administering HVEM:Fc fusion protein or soluble HVEM to collagen-induced arthritis in six-week-old DBA/1 mice (art recognized model of rheumatoid arthritis) inhibits inflammation (Figure 10, pages 56-57). The specification also discloses administering anti-HVEM antiserum in culture of RAJI B cells lines stimulates B cells proliferation (page 55). HVEM is expressed on both malignant and normal human T cells (page 48) and resting CD4+ T cells (page 54).

The specification does not teach how to make all HVEM polypeptide, all LTβR polypeptide, and all fusion protein, much less for inhibiting p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis* (claims 26-27, 36, 51-52) by administering a composition comprising *all* HVEM or *all* LTβR polypeptide such as all soluble HVEM polypeptide (claim 36), all fusion protein comprising HVEM or LTβR (claim 51) or all HVEM:Fc or LTβR:Fc polypeptide (claim 52) that binds to a p30 polypeptide having an apparent molecular weight of about 30 kDa as determined by SDS-PAGE and pI of about pI 7 to pI 8.5 that binds to HVEM or LTβR and a method of in inhibiting all p30 polypeptide mediated cellular response in vitro (claim 53). There is insufficient guidance as to the structure of *all* HVEM and LTβR polypeptide without the amino acid sequences. The specification discloses only HVEM and LTβR from mouse. With regard to the fusion protein (claim 51), there is insufficient guidance as to the structure of the fusion protein because the fusion partner other than Fc that fused to HVEM or LTβR is not adequately described. The specification disclosed Fc fusion protein comprising the extracellular domain of mouse HVEM fused to the Fc region of human IgG (HVEM:Fc or soluble HVEM polypeptide) or mouse LTβR fused to the Fc region of human IgG to form LTβR:Fc.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between

sequences and the current structure prediction methods is unreliable (See figure, entire document).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Mestas *et al* teach that there are a number of significant differences between mice and humans in delayed-type hypersensitivity, multiple sclerosis and caution is required when extrapolating results from mouse studies to the clinic (See entire document, page 2735, col. 2, differences in immune system biology, in particular). Given the indefinite number of undisclosed HVEM polypeptide, LTβR polypeptide and fusion protein, it is unpredictable which HVEM polypeptide LTβR polypeptide and fusion protein is effective for inhibiting all p30-mediated cellular response in vitro or in vivo. Because the amino acid sequences of all HVEM polypeptide, LTβR polypeptide and fusion protein are not enabled, the claimed methods of using said HVEM polypeptide, LTβR polypeptide and fusion protein are not enabled.

Further, there is insufficient in vivo working examples demonstrating that all soluble HVEM, LTβR polypeptide and/or fusion protein are effective for inhibiting p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis*. In fact, there is no in vivo working example demonstrating that soluble LTβR polypeptide could inhibit p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis* at the time of filing.

Fava *et al* (J Immunology 171: 115-126, 2003; 1449) teaches the specific p30 (LIGHT) inhibitor HVEM-Ig (soluble HVEM or fusion protein comprising HVEM fused to Ig) had no efficacy in the collagen-induced arthritis model (See page 123, col. 1, second paragraph, in particular). This is consistent with the CIA score at 28 days after mHVEM-Fc treatment in CIA model as shown in FIG 10 of instant application.

Tian *et al,* of record, teach that in experimentally induced organ specific autoimmune disease models, the initiating antigen is defined. However, an initiating target antigen has not yet defined in human T-cell mediated autoimmune disease such as MS or IDDM (See page 190, in particular). Tian *et al* further teach that animal models of T-cell-mediated autoimmune disease rely on specific MHC genotypes and the animals often genetically predisposed to developing polarized immune response, these are likely to contribute to their disease susceptibility as well as their amenability to immunotherapy. By contrast, human MHC types are highly polymorphic, and little is known about antigen processing and presentation in this context, as well as what

factors determine the nature of the immune response and possible long-term treatment (See page 193, column 1, in particular).

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. As such, further research would be required. In view of the quantity of experimentation necessary, the insufficient number of working examples, the unpredictability of the art, the insufficient guidance and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicants' arguments filed 4/19/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the p30 polypeptide is the same molecule as LIGHT (page 6). (2) The amended claim 26 recites that the composition that binds to a p30 polypeptide comprises an "HVEM or LTPR polypeptide" and that the p30 polypeptide-mediated cellular response comprises "inhibition of rheumatoid arthritis." The HVEM or LTPR polypeptide "binds to a p30 polypeptide" defined as "having an apparent molecular weight of about 30kDa as determined by SDS-PAGE and an isoelectric charge (pI) of about pI 7 - pI 8.5 and that binds HVEM or LTβR". The specification teaches how to identify compositions having the recited functions for practicing the claimed methods. (3) As to the guidance regarding "fusion protein," the specification discloses that Fc or LTβR can be used as a fusion partner (see, for example, page 24, lines 3-7 and page 39, lines 12-14). (4) As to functional fragments, the specification discloses that excluded sequences include fragments lacking the carboxyl terminal portion of the full length HVEM (page 23, lines 12-13). HVEM:FC has amino acids 1 to 205 of HVEM (page 21, lines 19-21). The specification exemplifies HVEM amino acids 1 to 205 as having the requisite activity (page 57 and 58, Examples 7 and 8). Additional HVEM and LTβR functional fragments can be readily identified. (5) Previous submitted exhibits A and B, publications by Tamada et al (J Clin. Invest 109: 549 (2002) and Nature Med 6: 283 (2000) indicated that blockade of LIGHT by soluble lymphotoxin β receptor (LTβR-Ig) ameliorates lethal graft-versus-host disease (GVHD). Exhibit 1 submitted herewith published by Fava et al (J Immunol 171: 115 (2003) describes a study in which treating a collagen-induced arthritis animal model with LTβR-Ig reduced the severity of arthritis damage and joint tissue damage. Thus the claimed methods are adequately described.

In response to applicant's argument that the specification teaches how to identify compositions having the recited functions for practicing the claimed methods, it is noted that the claimed method encompasses all HVEM and LTβR for inhibiting any p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis*. The specification discloses only administering Fc fusion protein comprising the extracellular domain of mouse HVEM fused to the Fc region of human IgG (HVEM:Fc or soluble HVEM polypeptide) to eight weeks old female BDF1 mice that has been immunized with OVA absorbed to alum inhibits inflammation or delayed-type hypersensitivity in mice as measured by increased footpad thickness (page 56, Figure 9). The specification further discloses administering HVEM:Fc fusion protein or soluble HVEM to collagen-induced arthritis in six-week-old DBA/1 mice (art recognized model of rheumatoid arthritis) inhibits inflammation (Figure 10, pages 56-57). The specification also discloses administering anti-HVEM antiserum in culture of RAJI B cells lines stimulates B cells proliferation (page 55). HVEM is expressed on both malignant and normal human T cells (page 48) and resting CD4+ T cells (page 54). However, the specification does not teach whether mouse HVEM or LTPR polypeptide binds to the human p30 polypeptide or human HVEM or LTPR polypeptide binds to mouse p30 polypeptide. The p30 polypeptides from other species are not even been cloned. Until the human p30 polypeptide or other species other than mouse has been identified and having the equivalent function as that of the moue p30 polypeptide (LIGHT), the specification merely invites one of skill in the art for further experimentation.

In response to applicant's argument that the Fc or LTβR as the fusion partner in the fusion protein for the claimed method, it is noted that the features upon which applicant relies (the fusion partners, i.e., Fc) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument about the functional fragment, it is noted that the features upon which applicant relies (the extracellular domain of HVEM) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument in item 5, there is insufficient in vivo working examples demonstrating that all soluble HVEM, LTβR polypeptide and/or fusion protein are

effective for inhibiting p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis*. In fact, there is no in vivo working example demonstrating that soluble LTβR polypeptide could inhibit p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis* at the time of filing.

Further, Fava *et al* (J Immunology 171: 115-126, 2003; 1449) teaches the specific p30 (LIGHT) inhibitor HVEM-Ig (soluble HVEM or fusion protein comprising HVEM fused to Ig) had no efficacy in the collagen-induced arthritis model (See page 123, col. 1, second paragraph, in particular). This is consistent with the CIA score at 28 days after mHVEM-Fc treatment in CIA model as shown in FIG 10 of instant application.

Tian *et al,* of record, teach that in experimentally induced organ specific autoimmune disease models, the initiating antigen is defined. However, an initiating target antigen has not yet defined in human T-cell mediated autoimmune disease such as MS or IDDM (See page 190, in particular). Tian *et al* further teach that animal models of T-cell-mediated autoimmune disease rely on specific MHC genotypes and the animals often genetically predisposed to developing polarized immune response, these are likely to contribute to their disease susceptibility as well as their amenability to immunotherapy. By contrast, human MHC types are highly polymorphic, and little is known about antigen processing and presentation in this context, as well as what factors determine the nature of the immune response and possible long-term treatment (See page 193, column 1, in particular).

Mestas *et al* teach that there are a number of significant differences between mice and humans in delayed-type hypersensitivity and multiple sclerosis, for example, and caution is required when extrapolating results from mouse studies to the clinic (See entire document, page 2735, col. 2, differences in immune system biology, in particular).

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

7. Claims 26-27, 36 and 51-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *all* HVEM polypeptide, all LTβR polypeptide, all fusion protein, and all functional fragment thereof for a method of inhibiting p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis* (claims 26-27, 36, 51-52) and a method of in inhibiting all p30 polypeptide mediated cellular response in vitro (claim 53).

The specification discloses only administering Fc fusion protein comprising the extracellular domain of mouse HVEM fused to the Fc region of human IgG (HVEM:Fc or soluble HVEM polypeptide) to eight weeks old female BDF1 mice that has been immunized with OVA absorbed to alum inhibits inflammation or delayed-type hypersensitivity in mice as measured by increased footpad thickness (page 56, Figure 9). The specification further discloses administering HVEM:Fc fusion protein or soluble HVEM to collagen-induced arthritis in six-week-old DBA/1 mice (art recognized model of rheumatoid arthritis) inhibits inflammation (Figure 10, pages 56-57). The specification also discloses administering anti-HVEM antiserum in culture of RAJI B cells lines stimulates B cells proliferation (page 55). HVEM is expressed on both malignant and normal human T cells (page 48) and resting CD4+ T cells (page 54).

With the exception of the specific composition comprising the specific polypeptide of mentioned above, there is adequately written description about the structure associated with functions of *all* HVEM polypeptide, all LTβR polypeptide, *all* fusion protein, and all functional fragment thereof for the claimed methods without the amino acid sequence. Further, the specification discloses only HVEM and LTβR from mouse, the other HVEM and LTβR polypeptide for the claimed method are not adequately described. Assuming the HVEM and LTβR from human are known, there is insufficient written description about the structure of all p30 polypeptide and whether human HVEM and human LTβR bind to mouse p30 (LIGHT) polypeptide or vice versa, in turn, effective for inhibiting p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis* (claims 26-27, 36, 51-52) and a method of in inhibiting *all* p30 polypeptide mediated cellular response in vitro (claim 53). As the fusion protein (claim 51), the fusion partners, i.e., Fc that fused to the HVEM or LTβR is not adequately described. As to the functional fragment (claim 51), the

"extracellular domain" of HVEM or LTβR is not recited in the claim. the "functional fragment" in claim 51 could be from any protein fragments other than HVEM or LTβR.

The specification discloses only administering mouse HVEM:Fc fusion protein or soluble HVEM to inhibit mouse p30 polypeptide mediated inflammation in collagen-induced arthritis. Given the lack of a written description of *any* additional representative species of HVEM, LTβR fusion protein, and functional fragment for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 4/19/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the recited HVEM and LTβR compositions of the claimed methods are defined structurally and functionally. As to structural features, the specification exemplifies HVEM and LTPR species having the requisite function, HVEM:Fc and LTβR:Fc. As to a structural relationship, HVEM and LTPR are both members of the TNFR superfamily with common sequence motifs having particular function. Furthermore, HVEM and LTβR both bind to p30 polypeptide. Since both HVEM:Fc and LTβR:Fc bind to p30 polypeptide, a common structure is likely present within the HVEM and LTβR proteins that mediates p30 polypeptide binding. In addition, because HVEM and LTPR both bind to a p30 polypeptide and inhibit binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTPR, HVEM and LTβR have a common function. Accordingly, such structures are likely to be related. Finally, in addition to the HVEM and LTβR exemplified species, the specification teaches peptide fragments, variants, mimetics, fusions of the particular species (see, for example, page 20, line 22, to page 23, line 25). One skilled artisan readily recognizes the nature of these various compositions based upon HVEM and LTPR and, as such, would be apprised of Applicant's invention.

In contrast to applicant's assertion that HVEM and LTβR have a common function simply because HVEM and LTβR both bind to a p30 polypeptide and inhibit binding of a cell

surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR, HVEM binds only to LIGHT whereas LTβR binds to both LT and LIGHT. As evident by the Fava *et al* reference (J Immunology 171: 115-126, 2003; 1449), while soluble LTβR inhibits inflammation associated with collagen-induced arthritis, the specific p30 (LIGHT) inhibitor HVEM-Ig (soluble HVEM or fusion protein comprising HVEM fused to Ig) had no efficacy in the collagen-induced arthritis model (See page 123, col. 1, second paragraph, in particular).

The specification discloses only administering Fc fusion protein comprising the extracellular domain of mouse HVEM fused to the Fc region of human IgG (HVEM:Fc or soluble HVEM polypeptide) to eight weeks old female BDF1 mice that has been immunized with OVA absorbed to alum inhibits inflammation or delayed-type hypersensitivity in mice as measured by increased footpad thickness (page 56, Figure 9). The specification further discloses administering HVEM:Fc fusion protein or soluble HVEM to collagen-induced arthritis in six-week-old DBA/1 mice (art recognized model of rheumatoid arthritis) inhibits inflammation (Figure 10, pages 56-57). The specification also discloses administering anti-HVEM antiserum in culture of RAJI B cells lines stimulates B cells proliferation (page 55). HVEM is expressed on both malignant and normal human T cells (page 48) and resting CD4+ T cells (page 54).

With the exception of the specific composition comprising the mouse HVEM:Fc for inhibiting mouse p30 polypeptide mediated inflammation, there is adequately written description about the structure associated with functions of *all* other HVEM polypeptide, all LTβR polypeptide, *all* fusion protein, and all functional fragment thereof for the claimed methods without the amino acid sequence. Further, the specification discloses only HVEM and LTβR from mouse, the other HVEM and LTβR polypeptide for the claimed method are not adequately described. Assuming the HVEM and LTβR from human are known, there is insufficient written description about the structure of all p30 polypeptide and whether human HVEM and human LTβR bind to mouse p30 (LIGHT) polypeptide or vice versa, in turn, effective for inhibiting p30 polypeptide-mediated cellular response wherein the cellular response comprising inhibition of *rheumatoid arthritis* (claims 26-27, 36, 51-52) and a method of in inhibiting *all* p30 polypeptide mediated cellular response in vitro (claim 53). As the fusion protein (claim 51), the fusion partners, i.e., Fc that fused to the HVEM or LTβR is not adequately described. As to the functional fragment (claim 51), the "extracellular domain" of HVEM or LTβR is not recited in the claim. the "functional fragment" in claim 51 could be from any protein fragments other than HVEM or LTβR.

The specification discloses only administering mouse HVEM:Fc fusion protein or soluble HVEM to inhibit mouse p30 polypeptide mediated inflammation in collagen-induced arthritis. Given the lack of a written description of *any* additional representative species of HVEM, LTβR fusion protein, and functional fragment for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

In response to applicant's argument that in addition to the HVEM and LTβR exemplified species, the specification teaches peptide fragments, variants, mimetics, fusions of the particular species (see, for example, page 20, line 22, to page 23, line 25), the specification on page 21 discloses deletion of one or more amino acids can also result in modification of the structure of the resultant molecule without significant altering its activity (e.g. LIGHT-t66). The HVEM:Fc fusion polypeptide is characterized as having the amino acids 1 through 205 of HVEM or the extracellular domain of HVEM (Example 12). The specification does not describe which amino acids within HVEM or LTβR could be substituted for which amino acids and maintains function as that of HVEM and LTβR. Other than the specific mouse HVEM:Fc comprising mouse HVEM extracellular domain fused to the human Fc domain, the other HVEM, LTβR, peptide fragments, variants and mimetics for the claimed method are not adequately described.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 26-27 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "HVEM and LTβR polypeptide"... that binds to ...a cell surface expressed HVEM or LTβR is ambiguous and indefinite because HVEM or LTβR polypeptide binds only to p30 polypeptide and **does not bind** to it self such as cell surface expressed HVEM or LTβR as recited in claims 26 (b) and 53 (b). The "or the cell surface expressed HVEM or LTβR" in claim 26 (b) should be deleted.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
July 23, 2004

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